

Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease

A Randomized Trial

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Background: Treatment of moderate or severe chronic obstructive pulmonary disease (COPD) with combinations of inhaled corticosteroids, long-acting β -agonists, and long-acting anticholinergic bronchodilators is common but unstudied.

Objective: To determine whether combining tiotropium with salmeterol or fluticasone–salmeterol improves clinical outcomes in adults with moderate to severe COPD compared with tiotropium alone.

Design: Randomized, double-blind, placebo-controlled trial conducted from October 2003 to January 2006.

Setting: 27 academic and community medical centers in Canada.

Patients: 449 patients with moderate or severe COPD.

Intervention: 1 year of treatment with tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone–salmeterol.

Measurements: The primary end point was the proportion of patients who experienced an exacerbation of COPD that required treatment with systemic steroids or antibiotics.

Results: The proportion of patients in the tiotropium plus placebo group who experienced an exacerbation (62.8%) did not differ from that in the tiotropium plus salmeterol group (64.8%; difference, -2.0 percentage points [95% CI, -12.8 to 8.8 percentage

points]) or in the tiotropium plus fluticasone–salmeterol group (60.0%; difference, 2.8 percentage points [CI, -8.2 to 13.8 percentage points]). In sensitivity analyses, the point estimates and 95% confidence bounds shifted in the direction favoring tiotropium plus salmeterol and tiotropium plus fluticasone–salmeterol. Tiotropium plus fluticasone–salmeterol improved lung function ($P = 0.049$) and disease-specific quality of life ($P = 0.01$) and reduced the number of hospitalizations for COPD exacerbation (incidence rate ratio, 0.53 [CI, 0.33 to 0.86]) and all-cause hospitalizations (incidence rate ratio, 0.67 [CI, 0.45 to 0.99]) compared with tiotropium plus placebo. In contrast, tiotropium plus salmeterol did not statistically improve lung function or hospitalization rates compared with tiotropium plus placebo.

Limitations: More than 40% of patients who received tiotropium plus placebo and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label inhaled steroids or long-acting β -agonists.

Conclusions: Addition of fluticasone–salmeterol to tiotropium therapy did not statistically influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD.

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Most patients with moderate or severe chronic obstructive pulmonary disease (COPD) experience chronic progressive dyspnea that is not alleviated by short-acting bronchodilators. It is therefore not surprising that many patients are treated with multiple inhaled medications to optimize their lung function and minimize symptoms (1). Published guidelines on COPD state that the goals of pharmacologic therapy should be to control symptoms, improve health status, and reduce the frequency of COPD exacerbations (2, 3), and many published guidelines advocate combining different classes of long-acting bronchodilators or inhaled steroids to achieve these goals (2, 3).

In the past several years, several studies have shown that treatment of COPD with the long-acting anticholinergic tiotropium (4–7); the long-acting β_2 -agonist salmet-

erol (8–10); or products that combine inhaled steroids and long-acting β_2 -agonists, such as fluticasone–salmeterol or budesonide–formoterol (11–14), improve dyspnea and quality of life and decrease exacerbation rates compared

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Context

Physicians use multiple medications to treat chronic obstructive pulmonary disease (COPD).

Contribution

In this multicenter trial, 449 adults with moderate or severe COPD were randomly assigned to receive tiotropium and placebo, tiotropium and salmeterol, or tiotropium and fluticasone–salmeterol for 1 year. About 63%, 65%, and 60% of patients, respectively, had exacerbations. The third group, but not the second group, had better lung function and fewer hospitalizations than the first group.

Caution

Many patients discontinued assigned medications.

Implications

Adding fluticasone–salmeterol to tiotropium may improve lung function and decrease hospitalizations, but it does not affect reduce exacerbations in patients with moderate or severe COPD.

—The Editors

with placebo. However, no studies have assessed whether therapy with a combination of these products provides greater clinical benefit than does therapy with these agents used alone.

β_2 -Agonists and anticholinergics work by different mechanisms to cause bronchodilation (15), and inhaled corticosteroids may have an anti-inflammatory effect in COPD (16). Thus, it makes theoretical and intuitive sense that combining these therapies might be more beneficial than therapy with 1 agent alone. However, safety concerns, such as side effects associated with long-term use of long-acting β_2 -agonists and inhaled corticosteroids, and economic issues related to the additional costs of these medications may argue against routine use of inhaled medication polypharmacy without evidence of efficacy. We therefore conducted a randomized, double-blind, placebo-controlled clinical trial to determine whether combining tiotropium with salmeterol or fluticasone–salmeterol produces greater improvements in clinical outcomes for adults with moderate or severe COPD compared with tiotropium therapy alone.

METHODS**Design**

We designed a parallel-group, 3-group, randomized, double-blind, placebo-controlled trial in patients with moderate or severe COPD that was conducted from October 2003 to January 2006. The study protocol has been published elsewhere (17). The research ethics boards of all participating centers approved the study, and all trial participants provided written informed consent.

Setting and Participants

We enrolled patients with diagnosed moderate or severe COPD from 27 Canadian medical centers. Twenty centers were academic hospital–based pulmonary clinics, 5 were community-based pulmonary clinics, and 2 were community-based primary care clinics. Eligible patients had to have had at least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomization. Additional inclusion criteria were age older than 35 years; a history of 10 pack-years or more of cigarette smoking; and documented chronic airflow obstruction, with an FEV₁–FVC ratio less than 0.70 and a postbronchodilator FEV₁ less than 65% of the predicted value.

We excluded patients with a history of physician-diagnosed asthma before 40 years of age; those with a history of physician-diagnosed chronic congestive heart failure with known persistent severe left ventricular dysfunction; those receiving oral prednisone; those with a known hypersensitivity or intolerance to tiotropium, salmeterol, or fluticasone–salmeterol; those with a history of severe glaucoma or severe urinary tract obstruction, previous lung transplantation or lung volume reduction surgery, or diffuse bilateral bronchiectasis; and those who were pregnant or were breastfeeding. Persons with a recent COPD exacerbation requiring oral or intravenous antibiotics or steroids were required to wait until treatment with these agents had been discontinued for 28 days before entering the study.

Randomization and Interventions

We randomly assigned patients to 1 of 3 treatment groups for 52 weeks: tiotropium (Spiriva [Boehringer Ingelheim Pharma, Ingelheim, Germany]), 18 μ g once daily, plus placebo inhaler, 2 puffs twice daily; tiotropium, 18 μ g once daily, plus salmeterol (Serevent [GlaxoSmithKline, Research Triangle Park, North Carolina]), 25 μ g/puff, 2 puffs twice daily; or tiotropium, 18 μ g once daily, plus fluticasone–salmeterol (Advair [GlaxoSmithKline]), 250/25 μ g/puff, 2 puffs twice daily.

Randomization was done through central allocation of a randomization schedule that was prepared from a computer-generated random listing of the 3 treatment allocations, blocked in variable blocks of 9 or 12 and stratified by site. Neither research staff nor patients were aware of the treatment assignment before or after randomization.

All study patients were provided with inhaled albuterol and were instructed to use it when necessary to relieve symptoms. Any treatment with inhaled corticosteroids, long-acting β_2 -agonists, and anticholinergics that the patient may have been using before entry was discontinued on entry into the study. Therapy with other respiratory medications, such as oxygen, antileukotrienes, and methylxanthines, was continued in all patient groups.

Tiotropium was administered by using a Handihaler device (Boehringer Ingelheim). Study drugs were administered through a pressurized metered-dose inhaler using a

spacer device (Aerochamber Plus, Trudell Medical, London, Ontario, Canada), and patients were taught the correct inhalation technique to ensure adequate drug delivery. The metered-dose inhalers containing placebo, salmeterol, and fluticasone–salmeterol were identical in taste and appearance, and they were enclosed in identical tamper-proof blinding devices. The medication canisters within the blinding devices were stripped of any identifying labeling. Adherence to therapy was assessed by weighing the returned inhaler canisters.

Measurements and Outcomes

The primary outcome was the proportion of patients in each treatment group who experienced a COPD exacerbation within 52 weeks of randomization. Respiratory exacerbations were defined, according to the 2000 Aspen Lung Conference Consensus definition, as “a sustained worsening of the patient’s respiratory condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD” (18). An acute change in regular COPD medications was defined as physician-directed, short-term use of oral or intravenous steroids, oral or intravenous antibiotics, or both therapies.

Secondary outcomes were the mean number of COPD exacerbations per patient-year; the total number of exacerbations that resulted in urgent visits to a health care provider or emergency department; the number of hospitalizations for COPD; the total number of hospitalizations for all causes; and changes in health-related quality of life, dyspnea, and lung function. Health-related quality of life was assessed by using the St. George’s Respiratory Questionnaire (19), dyspnea was assessed by using the Transitional Dyspnea Index (20) and the dyspnea domain of the Chronic Respiratory Disease Questionnaire (21), and lung function was assessed by measuring the FEV₁ according to established criteria of the American Thoracic Society.

Follow-up Procedures

Patients were monitored for exacerbations by monthly telephone calls. Exacerbations and all secondary outcomes were also assessed through patient visits at baseline and at 4, 20, 36, and 52 weeks after randomization. For every suspected exacerbation, we contacted both the patient and the patient’s treating physician to ensure that the medical encounter had been prompted by acute respiratory symptoms and a full report, including physician, emergency department, and hospital records that described the circumstances of each suspected exacerbation, was prepared. The assembled data from the visit for the suspected exacerbation were presented to a blinded adjudication committee for review, and the committee confirmed whether the encounter met the study definition of COPD exacerbation. For the purposes of the trial, we considered that a patient had experienced a new COPD exacerbation if he or she had not been receiving oral steroids and antibiotics for at least 14 days after the previous exacerbation.

Patients were followed for the full 52-week duration of the trial, and primary and secondary outcomes were recorded throughout the 1-year period regardless of whether patients had experienced an exacerbation or discontinued treatment with study medications. We did not break the study blinding for patients who prematurely discontinued treatment with study medications.

Adverse events were captured by the research coordinators through monthly patient telephone interviews and at scheduled patient visits by using checklists of potential side effects. Physicians rated events as expected or unexpected, and they were asked to rate event severity and attribute causality of adverse events to the study drugs.

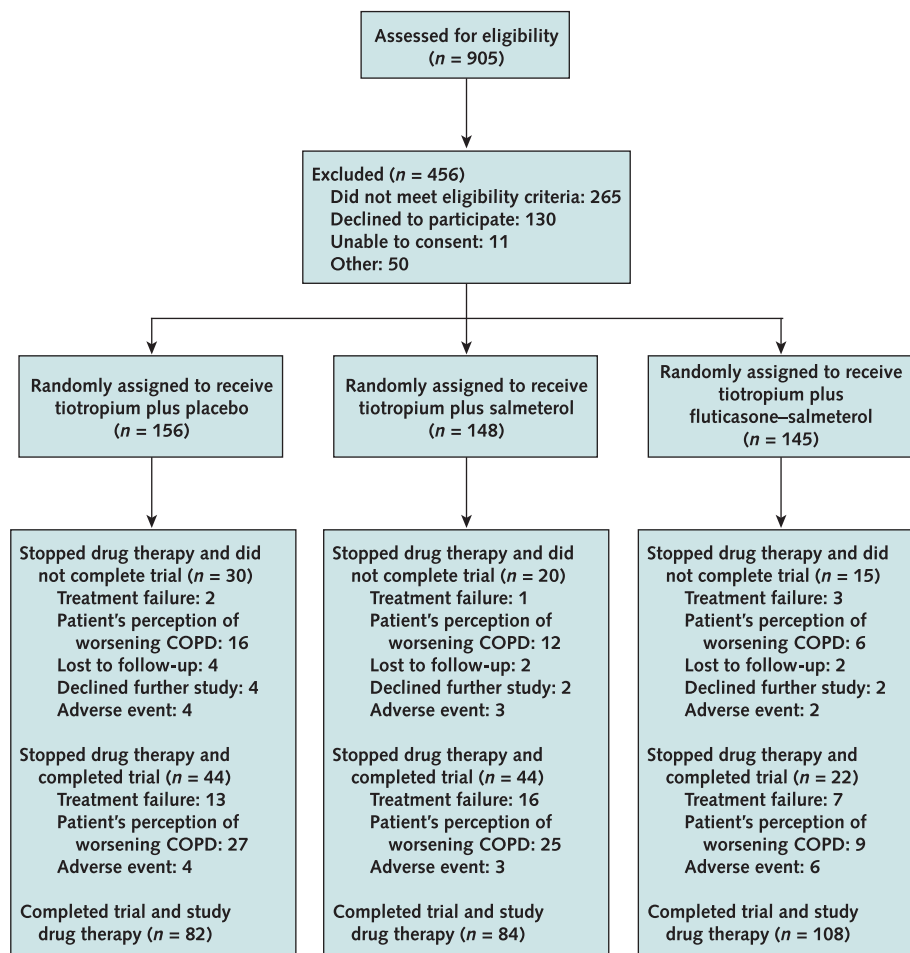
Statistical Analysis

We designed the study to detect an 18% absolute difference in the proportion of patients who had at least 1 exacerbation between the tiotropium plus placebo group and the other 2 treatment groups. We chose this risk reduction on the basis of published clinical trial data demonstrating that median rates of COPD exacerbation could be reduced by 25% in patients treated with inhaled steroids compared with those taking placebo (22). In addition, the trial steering committee, in consultation with a survey of 16 Canadian respirologists, determined that a 20% difference in the proportion of relapse at 1 year between the tiotropium plus placebo group and the tiotropium plus salmeterol group or tiotropium plus fluticasone–salmeterol group was the minimal clinically significant difference that would be important for the study to detect. Assuming a baseline risk for exacerbation of 55%, an 18% risk difference with an α value of 0.05, and 80% power, we required 130 patients per group. To allow for a 5% dropout rate (Lachin formula) (23), we required a sample size of 144 patients per group, or 432 patients in total.

The final analysis was conducted on an intention-to-treat basis by using SAS software, version 9.0 (SAS Institute, Inc., Cary, North Carolina). Two pairwise comparisons were planned to compare the tiotropium plus placebo group with the other 2 treatment groups. The study was not designed or powered to compare differences between the tiotropium plus salmeterol group and the tiotropium plus fluticasone–salmeterol group. The primary comparison of the proportion of exacerbations in the tiotropium plus placebo group versus the other 2 treatment groups was done by using an unadjusted chi-square test. A logistic regression procedure was then used to adjust the raw proportions of exacerbations by using clinically important covariates (study site, age, sex, severity of airflow obstruction at baseline, use of medication and home oxygen before study entry, current smoking status, and comorbid illnesses) that could influence outcomes. The statistician who performed the analysis was initially blinded to patient group assignments.

For the primary analysis, we conservatively assumed that patients who prematurely discontinued use of study

Figure 1. Study flow diagram.



COPD = chronic obstructive pulmonary disease.

medications and were lost to follow-up before having an exacerbation event did not have an event. Other trials that have examined COPD exacerbations as an outcome have made the same assumption (7, 24). However, we also performed 2 sensitivity analyses, in which we assumed that all patients who prematurely withdrew from the study had an exacerbation or that they had exacerbations at the same rate as those who continued in the study.

Analysis of the total number of COPD exacerbations per patient-year of observation was done according to methods using a weighted Poisson regression model approach that accounted for heterogeneity in exacerbation rates among patients by incorporating an overdispersion parameter (25). This intention-to-treat analysis retained patients in the group to which they were randomly assigned and counted exacerbations that occurred during the 1-year study period regardless of whether the patient continued to take study medications, as per Consolidated Standards of Reporting Trials (CONSORT) guidelines

(26). An alternative compliance analysis was also done that incorporated the overdispersion parameter and censored all patients after they prematurely stopped using study medications.

Continuous outcomes, such as the values for the St. George's Respiratory Questionnaire, the Transitional Dyspnea Index, and the FEV₁, were analyzed by using repeated-measures mixed models that provided estimates for the treatment minus placebo difference at 52 weeks, controlled for baseline, treatment, visit, and visit-by-treatment interaction effects. The frequencies of urgent visits and hospitalizations were compared by using incidence rate ratios that were estimated from weighted Poisson regression models. The Kaplan-Meier estimates of the time to first exacerbation were tested for significance by using the log-rank test. Subsequently, Cox proportional hazards modeling was done to adjust for baseline variables that may affect the time to next exacerbation. Because survival curves for tiotropium plus placebo and tiotropium plus salmeterol

crossed, the tiotropium plus salmeterol group was not included in the Cox proportional hazards models.

Role of the Funding Sources

The Canadian Institutes of Health Research and The Ontario Thoracic Society provided peer-reviewed funding for this study. The sponsors of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Sample

Nine hundred five patients were screened, and 629 (70%) were eligible for the study (Figure 1). Of these 629 patients, 130 declined to participate and 50 were excluded for other reasons (such as planned prolonged travel out of Canada during the study period). Four hundred fifty-one randomization numbers were assigned; however, 2 patients were withdrawn before undergoing randomization and never received study medications. One of these patients

was withdrawn because metastatic lung cancer was discovered on the day of the randomization visit, and 1 was withdrawn because her private insurance company would not provide health care coverage if she entered a clinical trial. Therefore, 449 patients underwent randomization. One hundred fifty-six patients were assigned to receive tiotropium plus placebo, 148 were assigned to receive tiotropium plus salmeterol, and 145 were assigned to receive tiotropium plus fluticasone-salmeterol. The 3 groups had similar baseline characteristics (Table 1). A similar proportion of patients in each group was receiving inhaled corticosteroids or inhaled corticosteroids and long-acting β_2 -agonist combination products at the time of randomization (77%, 79%, and 73% of patients in the tiotropium plus placebo, tiotropium plus salmeterol and tiotropium plus fluticasone-salmeterol groups, respectively).

During the 12-month trial, 7%, 6%, and 8% of patients in the tiotropium plus placebo, tiotropium plus salmeterol, and tiotropium plus fluticasone-salmeterol groups, respectively, enrolled in a pulmonary rehabilitation program; 3%, 1%, and 3%, respectively, quit smoking; 4%, 5%, and 5%, respectively, began using home oxygen; and

Table 1. Baseline Characteristics

Characteristic	Tiotropium Plus Placebo (n = 156)	Tiotropium Plus Salmeterol (n = 148)	Tiotropium Plus Fluticasone-Salmeterol (n = 145)
Mean age (SD), y	68.1 (8.9)	67.6 (8.2)	67.5 (8.9)
Women, %	46.2	42.6	42.1
White, %	97.4	98.0	99.3
Body mass index (SD), kg/m ²	27.6 (6.0)	27.2 (5.8)	27.8 (6.2)
Smoking status			
Current smoker, %	26.9	24.3	32.4
Pack-year history (SD), n	51.8 (28.0)	48.7 (27.1)	50.3 (23.1)
Duration of reported dyspnea (SD), y	11.3 (8.8)	10.7 (8.7)	10.3 (8.1)
Medication use, %			
Ipratropium	34.4	44.5	42.9
Tiotropium	57.8	55.5	46.4
Short-acting β_2 -agonists	77.9	82.2	80.0
Long-acting β_2 -agonists	11.7	19.2	17.9
Combination of inhaled steroid and long-acting β_2 -agonist	51.9	43.9	45.7
Inhaled corticosteroids	25.3	34.9	27.1
Antileukotrienes	2.0	2.7	2.9
Methylxanthines	7.1	11.6	5.7
Home oxygen	11.7	13.7	10.0
Influenza vaccine	74.8	74.0	77.3
Prebronchodilator lung function			
Mean FEV ₁ (SD), L	1.01 (0.38)	1.00 (0.44)	1.05 (0.38)
Mean percent predicted FEV ₁ (SD)	38.7 (12.9)	38.0 (13.1)	39.4 (11.9)
Mean FVC (SD), L	2.30 (0.69)	2.36 (0.80)	2.39 (0.75)
Mean FEV ₁ -FVC ratio (SD)	0.44 (0.11)	0.43 (0.12)	0.45 (0.12)
Postbronchodilator lung function			
Mean FEV ₁ (SD), L	1.08 (0.40)	1.08 (0.43)	1.12 (0.41)
Mean percent predicted FEV ₁ (SD)	42.1 (13.5)	41.2 (13.0)	42.2 (12.2)
Mean FVC (SD), L	2.50 (0.83)	2.51 (0.79)	2.51 (0.83)
Mean dyspnea index score (SD)	6.3 (1.8)	6.5 (1.9)	6.5 (2.0)
Comorbid conditions, %			
Hypertension	43.0	43.9	41.4
Coronary artery disease	16.0	21.0	22.8
Congestive heart failure	3.9	1.4	3.5
Cancer	5.8	9.5	6.9

Table 2. Exacerbations of Chronic Obstructive Pulmonary Disease and Health Care Utilization during 1 Year*

Outcome	Tiotropium plus Placebo (n = 156)	Tiotropium plus Salmeterol (n = 148)	Tiotropium plus Fluticasone-Salmeterol (n = 145)
Primary analysis†			
Patients with ≥1 acute exacerbation of COPD, n (%)	98 (62.8)	96 (64.8)	87 (60.0)
Absolute risk reduction compared with tiotropium plus placebo (95% CI), percentage points		-2.0 (-12.8 to 8.8)	2.8 (-8.2 to 13.8)
Sensitivity analysis 1‡			
Patients with ≥1 acute exacerbation of COPD, n (%)	117 (75.0)	107 (72.3)	96 (66.2)
Absolute risk reduction compared with tiotropium plus placebo (95% CI), percentage points		2.7 (-7.2 to 12.6)	8.8 (-1.5 to 19.0)
Sensitivity analysis 2§			
Patients with ≥1 acute exacerbation of COPD, n (%)	112 (71.8)	104 (70.3)	93 (64.1)
Absolute risk reduction compared with tiotropium plus placebo (95% CI), percentage points		1.5 (-8.7 to 11.7)	7.6 (-2.9 to 18.1)
Exacerbations of COPD			
All exacerbations, n	222	226	188
Duration of follow-up, patient-years	138.0	129.4	137.1
Mean exacerbations per patient-year, n	1.61	1.75	1.37
Incidence rate ratio compared with tiotropium plus placebo (95% CI)	-	1.09 (0.84 to 1.40)	0.85 (0.65 to 1.11)
Urgent physician or emergency department visits for COPD exacerbation			
Total, n	185	184	149
Incidence rate ratio compared with tiotropium plus placebo (95% CI)		1.06 (0.87 to 1.30)	0.81 (0.65 to 1.01)
Hospitalizations for acute exacerbations of COPD			
Total, n	49	38	26
Incidence rate ratio compared with tiotropium plus placebo (95% CI)		0.83 (0.54 to 1.27)	0.53 (0.33 to 0.86)
All-cause hospitalizations			
Total, n	62	48	41
Incidence rate ratio compared with tiotropium plus placebo (95% CI)		0.83 (0.57 to 1.21)	0.67 (0.45 to 0.99)

* COPD = chronic obstructive pulmonary disease.

† Assuming that all patients who were lost to follow-up did not have an exacerbation.

‡ Assuming that all patients who were lost to follow-up had an exacerbation.

§ Assuming that all patients who were lost to follow-up had exacerbations at the same rate as those who continued in the study.

|| Accounting for between-patient variability.

67%, 61%, and 72%, respectively, received the influenza vaccine.

Seventy-four of 156 patients (47%) in the tiotropium plus placebo group discontinued use of study medications before completing 1 year of therapy, compared with 64 of 148 patients (43%) in the tiotropium plus salmeterol group ($P = 0.54$) and 37 of 145 patients (26%) in the tiotropium plus fluticasone-salmeterol group ($P < 0.001$). Premature discontinuation of study medication was largely due to patients' perceived lack of medication efficacy or physician-directed discontinuation of study therapy because of a patient's deteriorating health status. Of the patients who discontinued use of study medications, 74% in the tiotropium plus placebo group, 70% in the tiotropium plus salmeterol group, and 54% in the tiotropium plus fluticasone-salmeterol group received an open-label inhaled steroid and long-acting β_2 -agonist combination inhaler for the remainder of the study.

Primary Outcome

The proportion of patients who experienced at least 1 COPD exacerbation during the trial did not significantly differ between the tiotropium plus placebo group and the 2 other treatment groups (Table 2). In the tiotropium plus placebo group, 62.8% of patients experienced an exacerbation,

compared with 64.8% in the tiotropium plus salmeterol group and 60.0% in the tiotropium plus fluticasone-salmeterol group. The absolute risk reduction was -2.0 percentage points (95% CI, -12.8 to 8.8 percentage points) for tiotropium plus salmeterol versus tiotropium plus placebo ($P = 0.71$) and 2.8 percentage points (CI, -8.2 to 13.8 percentage points) for tiotropium plus fluticasone-salmeterol versus tiotropium plus placebo ($P = 0.62$).

Table 2 shows the results of sensitivity analyses that made alternative assumptions for patients who prematurely withdrew from the trial. Results of the sensitivity analyses were statistically nonsignificant; however, shifts in the point estimates and 95% confidence bounds were in the direction favoring tiotropium plus salmeterol and tiotropium plus fluticasone-salmeterol.

The unadjusted odds ratio of risk for exacerbation was 1.03 (CI, 0.63 to 1.67) with tiotropium plus salmeterol versus tiotropium plus placebo and 0.85 (CI, 0.52 to 1.38) for tiotropium plus fluticasone-salmeterol versus tiotropium plus placebo. Adjustments for clinically important covariates (site, age, sex, severity of airflow obstruction at baseline, medication and home oxygen use before entering the study, current smoking status, and comorbid illnesses) did not appreciably change the odds ratios or CIs around the esti-

mates; adjusted odds ratios were 1.01 (CI, 0.59 to 1.73) and 0.84 (CI, 0.47 to 1.49), respectively.

Secondary Outcomes

Exacerbations per Patient-Year

The mean number of COPD exacerbations per patient-year of observation did not significantly differ between the tiotropium plus placebo group and the other 2 treatment groups. Patients who received tiotropium plus placebo experienced 1.61 exacerbations per patient-year of follow-up, compared with 1.75 exacerbations per patient-year in the tiotropium plus salmeterol group and 1.37 exacerbations per patient-year in the tiotropium plus fluticasone-salmeterol group (Table 2). The incidence rate ratio was 1.09 (CI, 0.84 to 1.40) for tiotropium plus salmeterol compared with tiotropium plus placebo ($P = 0.51$) and 0.85 (CI, 0.65 to 1.11) for tiotropium plus fluticasone-salmeterol versus tiotropium plus placebo ($P = 0.24$).

Alternative Compliance Analysis of Mean Number of Exacerbations per Patient-Year

An alternative compliance analysis was done in which patients were censored after they prematurely discontinued use of study medications. This analysis showed that patients who were randomly assigned to receive tiotropium plus placebo experienced 1.66 exacerbations per patient-year, compared with 1.78 exacerbations per patient-year in the tiotropium plus salmeterol group and 1.31 exacerbations per patient-year in the tiotropium plus fluticasone-salmeterol group. The incidence rate ratio was 1.07 (CI, 0.74 to 1.55) for tiotropium plus salmeterol versus tiotropium plus placebo ($P = 0.71$) and 0.79 (CI, 0.54 to 1.14) for tiotropium plus fluticasone-salmeterol versus tiotropium plus placebo ($P = 0.21$).

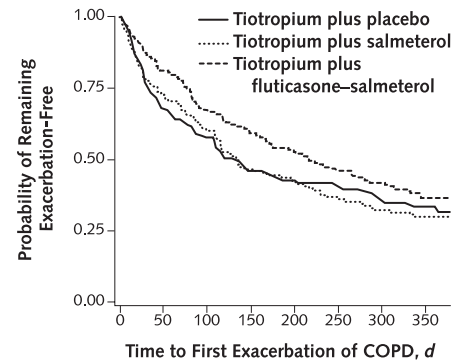
Time to First Exacerbation

The median time to first exacerbation was 130 days in the tiotropium plus placebo group, 128 days in the tiotropium plus salmeterol group, and 217 days in the tiotropium plus fluticasone-salmeterol group (Figure 2). These differences were not statistically significant. Compared with tiotropium plus placebo, tiotropium plus fluticasone-salmeterol did not statistically prolong the time to first exacerbation; the adjusted hazard ratio was 0.80 (CI, 0.60 to 1.08) ($P = 0.15$).

Hospitalizations

Patients treated with tiotropium plus fluticasone-salmeterol had lower rates of severe exacerbations of COPD requiring hospitalization than did patients treated with tiotropium plus placebo; the incidence rate ratio was 0.53 (CI, 0.33 to 0.86) ($P = 0.01$) (Table 2). All-cause hospitalizations were also reduced in patients treated with tiotropium plus fluticasone-salmeterol compared with patients treated with tiotropium plus placebo ($P = 0.04$) (Table 2). Similar significant benefits were not seen for the group

Figure 2. Kaplan–Meier estimates of the probability of remaining free of exacerbations, according to treatment assignment.



Patients at risk, <i>n</i>								
Tiotropium plus placebo	156	102	84	65	59	57	50	45
Tiotropium plus salmeterol	148	100	81	61	55	48	41	38
Tiotropium plus fluticasone-salmeterol	145	116	94	82	72	62	55	48

The unadjusted hazard ratio was 1.02 (95% CI, 0.77 to 1.37) for tiotropium plus placebo versus tiotropium plus salmeterol ($P = 0.87$) and 0.80 (CI, 0.60 to 1.08) for tiotropium plus placebo versus tiotropium plus fluticasone-salmeterol ($P = 0.15$). COPD = chronic obstructive pulmonary disease.

treated with tiotropium plus salmeterol compared with tiotropium plus placebo.

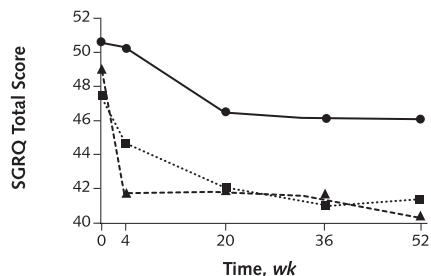
Health-Related Quality of Life

One year of therapy with tiotropium plus salmeterol or tiotropium plus fluticasone-salmeterol improved health-related quality of life significantly more than did therapy with tiotropium plus placebo. The 1-year change in total score on the St. George’s Respiratory Questionnaire was -4.5 points in the tiotropium plus placebo group, -6.3 points in the tiotropium plus salmeterol group ($P = 0.02$), and -8.6 points in the tiotropium plus fluticasone-salmeterol group ($P = 0.01$) (Figure 3).

Lung Function

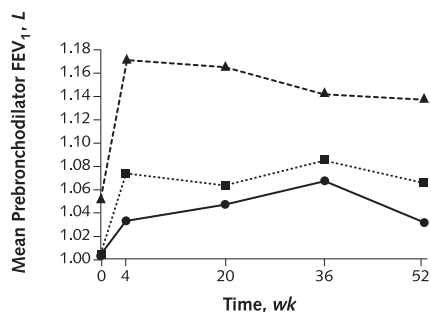
Tiotropium plus fluticasone-salmeterol improved the FEV₁ more than did tiotropium plus placebo (Figure 3). Over 52 weeks, the absolute prebronchodilator FEV₁ increased by 0.027 L in the tiotropium plus placebo group compared with 0.086 L in the tiotropium plus fluticasone-salmeterol group ($P = 0.049$), and the percent predicted FEV₁ increased by 1.3% in the tiotropium plus placebo group compared with 4.6% in the tiotropium plus fluticasone-salmeterol group ($P = 0.005$). Lung function was not significantly better in the tiotropium plus salmeterol group than in the tiotropium plus placebo group.

Figure 3. Changes in health-related quality of life and FEV₁ over 1 year.



Patients with valid observations at each time point, *n*

Tiotropium plus placebo	154	147	132	126	123
Tiotropium plus salmeterol	146	134	122	122	122
Tiotropium plus fluticasone-salmeterol	145	141	131	129	124



Patients with valid observations at each time point, *n*

Tiotropium plus placebo	152	141	128	123	120
Tiotropium plus salmeterol	146	137	117	117	115
Tiotropium plus fluticasone-salmeterol	142	141	129	125	122

—●— Tiotropium plus placebo —■— Tiotropium plus salmeterol —▲— Tiotropium plus fluticasone-salmeterol

Top. Scores on the St. George’s Respiratory Questionnaire (SGRQ). Lower scores indicate improvements in quality of life. $P = 0.02$ for tiotropium plus placebo versus tiotropium plus salmeterol at 52 weeks; $P = 0.01$ for tiotropium plus placebo versus tiotropium plus fluticasone-salmeterol at 52 weeks. **Bottom.** Mean prebronchodilator FEV₁. $P = 0.87$ for tiotropium plus placebo versus tiotropium plus salmeterol at 52 weeks; $P = 0.049$ for tiotropium plus placebo versus tiotropium plus fluticasone-salmeterol at 52 weeks.

Dyspnea

Dyspnea scores improved over 1 year of observation but did not significantly differ among the treatment groups. Mean transitional dyspnea index scores at 1 year were 1.78 (SD, 4.08) in the tiotropium plus placebo group, 1.40 (SD, 3.96) in the tiotropium plus salmeterol group ($P = 0.35$), and 1.84 (SD, 3.86) in the tiotropium plus fluticasone-salmeterol group ($P = 0.38$).

Deaths and Adverse Events

During the study, 4 patients (2.6%) in the tiotropium plus placebo group died, as did 6 patients (4.1%) each in

the tiotropium plus salmeterol and tiotropium plus fluticasone-salmeterol groups (Table 3). In total, 28 patients experienced serious adverse events associated with hospitalization (other than for COPD), admission to the intensive care unit, or death. Ten serious adverse events occurred in the tiotropium plus placebo group, 9 occurred in the tiotropium plus salmeterol group, and 9 occurred in the tiotropium plus fluticasone-salmeterol group.

DISCUSSION

We found that adding fluticasone-salmeterol or salmeterol to therapy with tiotropium did not reduce the proportion of patients who experienced 1 or more COPD exacerbations during 1 year. The addition of fluticasone-salmeterol to tiotropium therapy resulted in a 2.8-percentage-point absolute reduction in the percentage of patients who experienced at least 1 exacerbation during 1 year. Because our trial was powered to show a larger expected percentage difference in these proportions, we could not show a statistically significant difference in this outcome, if the difference is real and not due to chance.

Of note, treatment with tiotropium plus fluticasone-salmeterol improved clinically important secondary outcomes. The rates of hospitalizations for COPD exacerbations and all-cause hospitalizations were statistically lower in patients who received tiotropium plus fluticasone-salmeterol than in those who received tiotropium plus placebo. This finding suggests that although adding fluticasone-salmeterol to tiotropium therapy did not affect overall exacerbation rates, combined therapy of tiotropium plus fluticasone-salmeterol may modify the severity of exacerbations, so that these patients may be less likely to require hospitalization when they do experience exacerbations. In contrast, therapy with tiotropium plus salmeterol did not result in lower hospitalization rates.

Other important secondary outcomes, such as health-related quality of life and lung function, were also improved by adding fluticasone-salmeterol to tiotropium therapy. A difference of 4 points in total score on the St. George’s Respiratory Questionnaire has been shown to be clinically significant. Patients treated with tiotropium plus fluticasone-salmeterol experienced an improvement in total scores on the St. George’s Respiratory Questionnaire that was more than 4 points greater than that in those treated with tiotropium plus placebo, indicating that the differences between the 2 treatment groups in health-related quality of life were statistically and clinically significant.

An English-language article search of MEDLINE to November 2006 revealed several clinical trials that have demonstrated the efficacy of tiotropium (4–7), salmeterol (8–10), or combination products with inhaled steroids plus long-acting β_2 -agonists (11–14) when used individually for treating COPD. In addition, 2 recent studies with a crossover design have evaluated the effects of 2 weeks and

Table 3. Mortality and Adverse Event Rates

Adverse Event	Tiotropium plus Placebo (n = 156)	Tiotropium plus Salmeterol (n = 148)	Tiotropium plus Fluticasone-Salmeterol (n = 145)
All-cause deaths, n (%)	4 (2.6)	6 (4.1)	6 (4.1)
Serious adverse events, n (%)	10 (6.4)	9 (6.1)	9 (6.2)
Patients who stopped the trial because of an adverse event, n (%)	8 (5.1)	6 (4.1)	8 (5.5)
Patients with adverse events, n (%)			
Total	37 (23.7)	32 (21.6)	44 (30.3)
Respiratory failure leading to mechanical ventilation or death	7 (4.5)	3 (2.0)	2 (1.4)
Pneumonia leading to mechanical ventilation or death	0 (0)	1 (0.7)	1 (0.7)
Cancer (other than skin)	1 (0.6)	1 (0.7)	1 (0.7)
Myocardial infarction or acute arrhythmia	2 (1.3)	2 (1.4)	2 (1.4)
Dry or sore mouth	10 (6.4)	10 (6.8)	15 (10.3)
Oral candidiasis	0 (0)	1 (0.7)	6 (4.1)
Voice hoarseness	1 (0.6)	2 (1.4)	9 (6.2)
Tremor	0 (0)	2 (1.4)	1 (0.7)
Dizziness	3 (1.9)	3 (2.0)	1 (0.7)
Coughing on administration of study medications	2 (1.3)	3 (2.0)	0 (0)

6 weeks of therapy with tiotropium plus formoterol (a long-acting β -agonist) on lung function. However, these studies did not assess clinical outcomes other than daytime and nighttime albuterol use (27, 28). Thus, we believe that our study is the first clinical trial to evaluate clinically important outcomes in patients with COPD treated with combinations of different classes of agents, and our study provides clinical trial evidence to potentially support COPD guideline recommendations.

Our results are somewhat at odds with those of other studies and of a meta-analysis suggesting that treatment of COPD with the inhaled corticosteroid fluticasone may decrease mean rates of COPD exacerbation per patient-year (22, 29). However, these discrepancies may be due to differences among study analytic techniques rather than actual biological differences. We used recommended techniques to analyze the mean number of exacerbations per patient-year by performing an intention-to-treat analysis and using a weighted Poisson regression model that provides a more accurate estimation of the effect of a medication on exacerbations by accounting for all sources of variability (25). However, this type of analysis, although statistically correct, widens the CIs around estimates of mean exacerbation rates. Our results show a tendency toward fewer exacerbations per patient-year in the group treated with tiotropium plus fluticasone-salmeterol, and if our sample had been larger, this difference, if real, may have become statistically significant.

An important consideration in a trial that does not find a statistically significant treatment effect for the primary outcome is whether the negative findings were due to a true absence of clinically important effects or a lack of statistical power. The CIs for our primary outcome of the proportion of patients who experienced a COPD exacerbation, and for the associated sensitivity analyses, can be used to determine the effect size that can be “ruled out” by our results (Table 2). For the comparison of tiotropium

plus placebo with tiotropium plus fluticasone-salmeterol, the point estimate for the absolute difference in exacerbation proportions varies from 2.8 percentage points favoring tiotropium plus fluticasone-salmeterol (assuming that patients who withdrew had no exacerbations) to 8.8 percentage points favoring tiotropium plus fluticasone-salmeterol (assuming that all patients who withdrew early had an exacerbation), and the 95% CIs range from 1.5 to 8.2 percentage points favoring tiotropium plus placebo and from 13.8 to 19.0 percentage points favoring tiotropium plus fluticasone-salmeterol. Of note, the 19-percentage point difference in exacerbation proportions favoring tiotropium plus fluticasone-salmeterol seen in the sensitivity analysis is the largest possible effect that can be consistent with the data; however, this difference, if real, might be clinically significant.

A potential limitation of our study is that more patients in the tiotropium plus placebo and the tiotropium plus salmeterol groups prematurely stopped taking study medications compared with patients in the tiotropium plus fluticasone-salmeterol group. Many patients stopped using the study medications because of a perceived lack of efficacy, and many crossed over to open-label fluticasone-salmeterol on the advice of their physicians. Study inhalers were identical in taste and appearance, and blinding devices were all returned intact; it is therefore unlikely that patients prematurely discontinued use of study medications because they realized that they were not receiving fluticasone-salmeterol.

Other clinical trials in COPD have dealt with the issue of differential compliance by dropping patients from the trial when they discontinued use of study medications. These trials did not record exacerbations that occurred after use of study medications was stopped (12, 14, 22). In contrast, we continued to follow patients for the full duration of the trial, even after they discontinued use of study medications, and we recorded subsequent exacerbations in

our intention-to-treat analysis, as recommended in the CONSORT guidelines (26). This unavoidable crossover effect may have diluted differences in the mean number of exacerbations per patient-year among the 3 groups. However, a secondary compliance analysis of our results, in which patients were censored when they prematurely discontinued use of study medications, still failed to show statistically significant differences in mean exacerbation rates per patient-year.

The fact that we did observe significant positive effects in quality of life, lung function, and hospitalization rates for patients who received tiotropium plus fluticasone–salmeterol compared with patients who received tiotropium plus placebo in the intention-to-treat analysis (even though more than one third of the patients in the latter group crossed over to open-label fluticasone–salmeterol for at least part of the study) argues for the strength of the beneficial effect of tiotropium plus fluticasone–salmeterol on these outcomes.

An important consideration when deciding whether to treat patients with COPD with fluticasone–salmeterol is that patients with advanced COPD are often elderly, and long-term treatment with inhaled corticosteroids has been associated with reductions in bone mineral density and osteoporosis in these patients (30). The clinical benefits of combining these drug classes must be balanced against the additional expense and potential inconvenience of adding another inhaler to an already complex treatment regimen (31). Nonetheless, our findings suggest that combined therapy with fluticasone–salmeterol plus tiotropium may have beneficial effects on quality of life, lung function, and hospitalizations without an increase in serious adverse events over the course of 1 year. Further methodologically rigorous, large studies are required to support our findings and to determine whether combined therapy with fluticasone–salmeterol plus tiotropium leads to definitive improvements in rates of COPD exacerbation.

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References

- Jackevicius CA, Chapman KR. Prevalence of inhaled corticosteroid use among patients with chronic obstructive pulmonary disease: a survey. *Ann Pharmacother*. 1997;31:160-4. [PMID: 9034414]
- Canadian Thoracic Society. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2003. *Can Respir J*. 2003;10 Suppl A:11A-65A. [PMID: 12861361]
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease. Accessed at www.goldcopd.com on 10 May 2006.
- Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J*. 2002;19:217-24. [PMID: 11866001]
- Dutch/Belgian Tiotropium Study Group. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J*. 2002;19:209-16. [PMID: 11871363]
- Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ Jr, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest*. 2002;122:47-55. [PMID: 12114338]
- Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med*. 2005;143:317-26. [PMID: 16144890]
- Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med*. 1997;155:1283-9. [PMID: 9105068]
- Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest*. 1999;115:957-65. [PMID: 10208192]
- Rennard SI, Anderson W, ZuWallack R, Broughton J, Bailey W, Friedman M, et al. Use of a long-acting inhaled beta2-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;163:1087-92. [PMID: 11316640]
- Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166:1084-91. [PMID: 12379552]
- Szafarski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21:74-81. [PMID: 12570112]
- Hanania NA, Darken P, Horstman D, Reiser C, Lee B, Davis S, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest*. 2003;124:834-43. [PMID: 12970006]
- TRial of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2003;361:449-56. [PMID: 12583942]
- Campbell S. For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base. *Arch Intern Med*. 1999;159:156-60. [PMID: 9927098]
- Pauwels R. Inhaled glucocorticosteroids and chronic obstructive pulmonary disease: how full is the glass? [Editorial]. *Am J Respir Crit Care Med*. 2002;165:1579-80. [PMID: 12070055]
- Aaron SD, Vandemheen K, Fergusson D, FitzGerald M, Maltais F, Bourbeau J, et al. The Canadian Optimal Therapy of COPD Trial: design, organization and patient recruitment. *Can Respir J*. 2004;11:581-5. [PMID: 15611808]
- Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest*. 2000;117:398S-401S. [PMID: 10843984]
- Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992;145:1321-7. [PMID: 1595997]
- Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest*. 1984;85:751-8. [PMID: 6723384]
- Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax*. 1987;42:773-8. [PMID: 3321537]
- Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ*. 2000;320:1297-303. [PMID: 10807619]
- Lachin JM. Introduction to sample size determination and power analysis for clinical trials. *Control Clin Trials*. 1981;2:93-113. [PMID: 7273794]
- Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med*. 2003;348:2618-25. [PMID: 12826636]
- Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2006;173:842-6. [PMID: 16439716]
- CONSORT GROUP (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Intern Med*. 2001;134:657-62. [PMID: 11304106]
- van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J*. 2005;26:214-22. [PMID: 16055868]
- van Noord JA, Aumann JL, Janssens E, Verhaert J, Smeets JJ, Mueller A, et al. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest*. 2006;129:509-17. [PMID: 16537846]
- Alsaedi A, Sin DD, McAlister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. *Am J Med*. 2002;113:59-65. [PMID: 12106623]
- Lung Health Study Research Group. Loss of bone density with inhaled triamcinolone in Lung Health Study II. *Am J Respir Crit Care Med*. 2004;170:1302-9. [PMID: 15374846]
- Calverley PM. Long-acting inhaled bronchodilators in COPD: how many drugs do we need? [Editorial]. *Eur Respir J*. 2005;26:190-1. [PMID: 16055864]

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